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EXAMINER

KERR, KATHLEEN M

ART UNIT PAPER NUMBER

1652

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/976,059	Applicant(s) FARNET ET AL.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 June 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 25-45 is/are pending in the application.
- 4a) Of the above claim(s) 27,28,30,35,36,38,39,41 and 45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 29,31,32 and 42 is/are rejected.
- 7) ☒ Claim(s) 25,26,33,34,37,40,43 and 44 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/27/04, 1/14/02</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on September 26, 2003), Applicants filed a response and amendment received on February 27, 2004 (corrected on June 14, 2004). Said amendment cancelled originally filed claims 1-24 and added new claims 25-45. Thus, Claims 25-45 are pending in the instant Office action.

Applicant's attention is drawn to the rules for making amendments to the specification and the claims (see 37 C.F.R. § 1.121, as amended on June 30, 2003 (see *68 Fed Reg. 38611*, June 30, 2003)). In particular, only one submission of amended claims and/or amendment specification should be filed with markings to show changes directly on said amendment.

Election

2. Applicant's election with traverse of SuperGroup A, SEQ ID NO: 15 (ORF 14), in the reply filed on February 27, 2004 is acknowledged. The traversal is on the ground(s) that products and methods related to ORFs 12, 13, 14, and 17 (SEQ ID NOs:13, 14, 15, and 18, respectively) should be examined together because they are structurally related proteins, all being NRPSs and sharing structural motifs. This is not found persuasive because the pending claims are drawn to exact SEQ ID NOs; therefore, it is this structural feature that must be considered and it is not the same for the different SEQ ID NOs. Applicant also argues that examining these four ORFs would be reasonable in a single application; the Examiner disagrees due to the enormous length of these proteins (>8000 amino acids long) requiring extensive searching time in sequence databases for even a single sequence. Applicant also comments that

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methods of use should be grouped together with the DNA products; the Examiner notes that these claims may be subject to rejoinder as previously noted.

The requirement is still deemed proper and is therefore made FINAL. Claims 27, 28, 30, 35, 36, 38, 39, 41, and 45 are drawn to non-elected subject matter and are withdrawn from consideration as non-elected inventions (Claim 45 may be subject to rejoinder). Claims 25, 26, 29, 31-34, 37, 40, and 42-44 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application Nos. 60/239,924 and 60/283,296 filed on October 13, 2000 and April 17, 2001 as requested in the declaration and the first lines of the specification. The earliest priority document, 60/239,924, teaches SEQ ID NO:1.

The instant application is also granted the benefit of priority for the U.S. non-Provisional Application No. 09/910,813 filed on July 24, 2001 as requested in the declaration and the first lines of the specification. Since no mention of lineage is noted in the priority request, the instant application is considered a continuation-in-part of 09/910,813.

Information Disclosure Statement

4. The information disclosure statements filed on January 14, 2004 and February 27, 2004 has been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

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Compliance with the Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2).

However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

- a) In Figures 3A, 3C, and 5B, amino acid sequences are disclosed without benefit of SEQ ID NOs. The Examiner notes that the SEQ ID NO referenced for Figure 5B does not describe the 5 amino acid peptide found in the figure.
- b) In paragraph [0115], a 7 amino acid sequence is disclosed without benefit of a SEQ ID NO.
- c) In paragraph [0123], several short peptides are disclosed without benefit of SEQ ID NOs; the Examiner notes that any peptide \geq 4 amino acids must comply with the sequence rules.
- d) In paragraph [0125], the iron-binding motif peptide must be identified by a SEQ ID NO.
- e) In paragraph [0130], 2 PCR primers are disclosed without benefit of SEQ ID NOs.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

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6. For the record, the Examiner comments that the amended sequence listing has been deemed to NOT introduce new matter. As noted previously, all of the encoded proteins disclosed (ORFs 1-33 in SEQ ID NOs:2-34) have support based on the exact encoding by SEQ ID NO:1, which was originally filed, in combination with the encoded protein ranges disclosed in the text of the specification as originally filed.

Objections to the Specification

7. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

--Gene Encoding a Nonribosomal Peptide Synthetase for the Production of Ramoplanin--

8. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the full name of the type of enzyme, a nonribosomal peptide synthetase (NRPS), and the source species, *Actinoplanes sp.*, for completeness.

9. Figure 2C is objected to for a typographical error. The "L-HPG" component of the ring in the top left, between D-Ala and L-HAsn, should be ---CHPG--- as disclosed in paragraph [0005] and as depicted (note Cl attached to the phenyl ring in the figure). Correction is required.

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10. The specification is objected to for having incomplete/unclear references as follows:

- a) In paragraph [0030], “Du *et al.* 1998”
- b) In paragraph [0080], “Grim” is misspelled; the correct spelling is ---Grimm---
- c) In paragraph [0080], “Woon” is not the correct author; the authors of the noted citation are Huang *et al.*
- d) In paragraph [0124], “Ullah *et al.* 1998” and “Baleman *et al.* 2000”
- e) In paragraph [0125], “Baleman *et al.* 2000” and “Hoffman *et al.* 1999”

If full citations are found elsewhere in the specification, full citations should be inserted at the above locations. If full citations are not found elsewhere in the specification, these citations must be deleted from the specification, particularly in light of the “incorporation by reference” statement at the end of the specification incorporating all mentioned references full by reference.

11. The specification is objected to for unclear data in the table on pages 35-41.

- a) The first column, presently unlabeled, should be labeled as “ORF”.
- b) An additional column noting the correlation to SEQ ID NOs would be helpful.
- c) ORF 3 on page 35 is not 321 amino acids but is disclosed as 336 amino acids (see SEQ ID NO:4 as encoded by SEQ ID NO:1 and paragraph [0040]).
- d) ORF 33 (partial) is missing from the table (see SEQ ID NO:34 as encoded by SEQ ID NO:1 and paragraph [0040]).

Correction is required.

12. The specification is objected to for having an unclear amendment. The replacement paragraph that begins on page 4 is described in the comments as being changed to “five or more”; however, this amendment is not found in the paragraph. The Examiner agrees that such an amendment would be supported by the specification as originally filed.

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Objections to the Claims

13. Claims 25, 26, and 31-34 are objected to for containing non-elected subject matter.

14. Claims 25, 26, 31-34, 37, 43, and 44 are objected to for having an improper Markush group. In a proper Markush group, the members must share unity of invention; “broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility” (see M.P.E.P. § 803.02). In Claim 25, a generic, common utility disclosed for the Markush members is that the nucleic acids encode products which synthesize ramoplanin; however, the *specific* utility for each ORF is distinct as depicted in Figure 2A or in the Table wherein ORF13 catalyzes reactions of different intermediates than does ORF14 than does ORF12 and wherein ORF17 is described as a threonine-specific adenylate ligase. Thus, the Markush group members of Claim 25 have a distinct utility for making distinct intermediates in the ramoplanin biosynthetic pathway and are improper in a Markush group together. The same reasoning is relevant to the improper Markush members of the group in Claim 37.

15. Claims 26, 29, 31-34, and 37 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

a) Claim 26 does not further limit Claim 25 because Claim 26 encompasses this exact subject matter since only these four domains are described as being in SEQ ID NO:15 on page 43 of the specification.

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- b) Claim 29 limits Claim 25 to only the elected subject matter - nucleic acid encoding a domain of SEQ ID NO:15. Since Claim 25 is already limited by Applicant's election, Claim 29 cannot further limit Claim 25.
- c) Claims 31-34 do not further limit Claim 26 because Claim 26 encompasses this exact subject matter due to the definitions of the domains on page 43 of the specification. The Examiner notes that the language in Claims 31-34 does not limit the subject matter to encoding, for example, the condensation domain 7458-7925 of SEQ ID NO:15, but merely defines the domains of Claim 26. To limit the claim to require these particular portions, the language must read ---wherein said nucleic acid [not said condensation domain] comprises ...---
- d) Claim 37 does not further limit Claim 26 because Claim 26 encompasses this exact subject matter due to the definitions of the domains on page 43 of the specification.

The Examiner notes that Claim 40 does further limit Claim 29 because while Claim 29 limits to any domain of SEQ ID NO:15, Claim 40 requires the full coding sequence of SEQ ID NO:1 that encodes SEQ ID NO:15. Claim 40 is similar to Claim 42, except that Claim 42 requires the exact encoding DNA while Claim 40 allowed for degeneracy variation.

16. Claim 40 is objected to for depending from an objected claim.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claim 29 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase “**an** amino acid sequence of SEQ ID NO:15” (emphasis added) is unclear because “an” refers to more than one sequence and the SEQ ID NO refers a single amino acid sequence.

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18. Claim 42 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 42 is confusing since it depends from a cancelled claim. It will be examined herein as if it depended from Claim 25 (the first claim). Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 31 and 32 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In Claim 31, the range of 1-470 for SEQ ID NO:15 is considered new matter; a range of 1-486 is found in page 43. In Claim 32, the range of 7296-8380 of SEQ ID NO:15 is considered new matter; a range of 7926-8380 is found on page 43. Applicant is required to delete the alleged new matter or to cite clear support (page and line number) where support can be found for the above alleged new matter in the specification as originally filed.

Additional Art of Record

20. The following are cited by the Examiner to complete the record:
- a) USPAP 2003/0054353 is the PGPubs document of 09/910,813, claimed as a priority document herein. While NRPS-encoding DNA is disclosed as being isolated (see Example 1), there is no indication that any DNA encoding SEQ ID NO:15 has been isolated (see Table 1 on page 8).
 - b) WO 02/31155 is the related international application.
 - c) GenBank Accession Number AX417445 (June, 2002) is a GenBank submission of SEQ ID NO:1 from WO 02/31155 which is identical to SEQ ID NO:1 in the instant application.
 - d) WO 03/089641 (Farnet *et al.*) is a related international application.
 - e) Mootz *et al.* (Curr Opin Biotechnol. (August, 1999) 10(4): 341-348) is a prior art review article about NRPSs.

Examiner's Comments

21. The Examiner notes that the pending claims meet the requirements for written description, enablement, and utility. The instant claims are drawn to nucleic acid sequences comprising at least specific portions (domains) of ORF14 (see Figure 2A) ramoplanin NRPS, which domains are defined in the specification on page 43. Within the claimed scope, there is no variability in the nucleic acid sequence over the length of the domain (specific structure) and the function is governed by inherency as well as the name of the domain (condensation domain, etc.). The art is replete with examples of using domains of NRPSs for the production of novel nonribosomal peptides, many of which have been found useful as therapeutics.

Conclusion

22. Claims 25, 26, 33, 34, 37, 40, and 43-44 are objected to; Claims 29, 31, 32, and 42 are rejected.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931.

The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Primary Examiner
Art Unit 1652

September 6, 2004